Synthesis of 5,6- and 5,7-Dichloro-3-methyl-4*H*-1,4-benzothiazines and their Conversion into Sulfones

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A one pot synthesis of 5,6- and 5,7-dichloro-3-methyl-4*H*-1,4-benzothiazines is reported by the condensation and oxidative cyclization of 2-amino-3,4- and 3,5-dichlorobenzenethiols with β-dicarbonyl compounds. The oxidation of 4*H*-1,4-benzothiazines by 30% hydrogen peroxide in glacial acetic acid has provided the corresponding sulfones. The effect of the conversion of the sulfide linkage to sulfone is discussed. The structure of all the newly synthesized compounds has been confirmed by elemental analysis and spectral studies.

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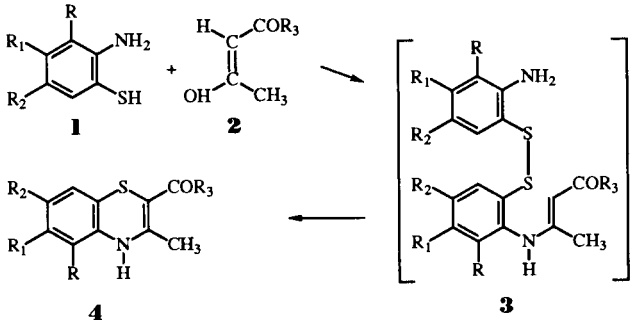
4*H*-1,4-Benzothiazines possess a wide spectrum of pharmacological/biological activities similar to phenothiazines [1,2] due to the presence of a fold along the nitrogen sulfur axis which is one structural specificity to impart similar pharmaceutical/biological activities [3-11]. The oxidation of the sulfide linkage in 4*H*-1,4-benzothiazines to 4*H*-1,4-benzothiazinesulfones forms an interesting series of heterocyclic compounds not only from the industrial [12] and medicinal [13-18] point of view but also for structural investigations.

In continuation to our programs to synthesize novel pharmaceutical heterocycles it is worthwhile to report a one pot reaction to synthesize the hitherto unknown title compounds and their conversion into sulfones.

5,6- And 5,7-dichloro-3-methyl-4*H*-1,4-benzothiazines have been synthesized by a one pot reaction involving the condensation and oxidative cyclization of 2-amino-3,4-/3,5-dichlorobenzenethiols **1** with dicarbonyl compounds **2** in DMSO. The reaction is believed to proceed through the formation of an intermediate enaminoketone (Scheme 1).

Scheme 1



1 **2** **3** **4**

R = Cl, H
R_1 = Cl, H
R_2 = Cl, H
R_3 = CH_3, OCH_3, OC_2H_5, $C_6H_4Cl(p)$, $C_6H_4Br(p)$, $C_6H_4F(p)$, $C_6H_4CH_3(p)$, $C_6H_4OCH_3(p)$, $C_6H_4OCH_3(m)$, $C_6H_3(OCH_3)_2(m,p)$

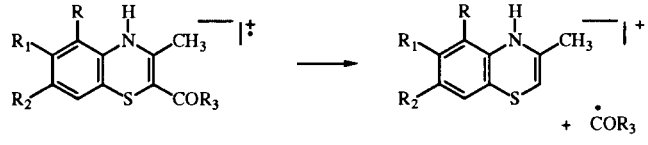
4*H*-1,4-Benzothiazinesulfones have been prepared by the oxidation of 4*H*-1,4-benzothiazine with 30% hydrogen peroxide in glacial acetic acid (Scheme 2).

Scheme 2

4 **5**

2-Aminobenzenethiol required in the synthesis of the title compounds has been prepared by the method reported [19].

Scheme 3



EXPERIMENTAL

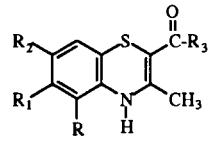
All melting points are uncorrected. The purity was checked by thin layer chromatography using non-polar solvents. The ir spectra of the benzothiazines and their sulfones have been recorded on a Perkin-Elmer spectrophotometer Model 577 in potassium bromide discs as well as in carbon tetrachloride. The ^1H nmr spectra were recorded at 90 MHz Jeol FX 90Q FT NMR spectrophotometer in DMSO-d_6 using TMS as an internal standard. Mass spectra of the 4*H*-1,4-benzothiazines were scanned on a Jeol JMSD-300 mass spectrometer at 70 eV and 100 μ amp ionizing current.

Preparation of Substituted 5,6-/5,7-Dichloro-3-methyl-4*H*-1,4-benzothiazines.

To the stirred suspension of β-diketone/β-ketoester **2** (0.01 mole) in DMSO (5 ml) was added 3,4-/3,5-dichloro-2-aminobenzenethiol **I** (0.01 mole) and the resulting mixture was refluxed for 15 minutes. The reaction mixture was concentrated, cooled down to room temperature and filtered. The product obtained was washed with petroleum ether and crystallized from methanol. The physical and analytical data of 4☆1,4-benzothiazines are given in Table 1.

Table 1

Physical Data of 4*H*-1,4-Benzothiazines **4a-o**



	Compound				MP	Yield	Molecular	% Calcd./Found		
	R	R_1	R_2	R_3	°C	%	Formula	C	H	N
I	II	III	IV	V	VI	VII	VIII	IX	X	XI
4a	Cl	Cl	H	CH_3	102-105	42	$C_{11}H_9NSOCl_2$	48.17 48.40	3.72 3.74	5.10 5.07
4b	Cl	H	Cl	CH_3	147-151	80	$C_{11}H_9NSOCl_2$	48.17 47.94	3.72 3.70	5.10 5.13
4c	Cl	Cl	H	OCH_3	130-132	58	$C_{11}H_9NSO_2Cl_2$	45.51 45.73	3.10 3.12	4.82 4.80
4d	Cl	H	Cl	OCH_3	112-115	67	$C_{11}H_9NSO_2Cl_2$	45.51 45.29	3.10 3.08	4.82 4.84
4e	Cl	Cl	H	OC_2H_5	94-96	62	$C_{12}H_{11}NSO_2Cl_2$	47.36 47.58	3.61 3.63	4.60 4.62
4f	Cl	H	Cl	OC_2H_5	98-101	73	$C_{12}H_{11}NSO_2Cl_2$	47.36 47.14	3.61 3.59	4.60 4.58
4g	Cl	Cl	H	C_6H_4Cl (*p*)	161-163	66	$C_{16}H_{10}NSOCl_3$	51.82 51.57	2.69 2.70	3.77 3.75
4h	Cl	H	Cl	C_6H_4Cl (*p*)	128-130	54	$C_{16}H_{10}NSOCl_3$	51.82 52.07	2.69 2.68	3.77 3.75
4i	Cl	Cl	H	C_6H_4Br (*p*)	151-153	43	$C_{16}H_{10}NSOCl_2Br$	46.26 46.46	2.40 2.41	3.37 3.35
4j	Cl	H	Cl	C_6H_4Br (*p*)	146-151	62	$C_{16}H_{10}NSOCl_2Br$	46.26 46.04	2.40 2.39	3.37 3.39
4k	Cl	Cl	H	C_6H_4F (*p*)	104-106	46	$C_{16}H_{10}NSOCl_2F$	54.23 54.47	2.82 2.81	3.95 3.97
4l	Cl	Cl	H	$C_6H_4CH_3$ (*p*)	130-133	52	$C_{17}H_{13}NSOCl_2$	58.28 58.04	3.71 3.69	4.00 4.02
4m	Cl	Cl	H	$C_6H_4OCH_3$ (*p*)	114-117	43	$C_{17}H_{13}NSO_2Cl_2$	55.73 55.48	3.55 3.57	3.82 3.84
4n	Cl	Cl	H	$C_6H_4OCH_3$ (*m*)	139-141	49	$C_{17}H_{13}NSO_2Cl_2$	55.73 55.98	3.55 3.57	3.82 3.80
4o	Cl	Cl	H	$C_6H_3(OCH_3)_2$ (*m,p*-)	151-155	76	$C_{18}H_{15}NSO_3Cl_2$	54.54 54.27	3.78 3.80	3.53 3.51

Preparation of Substituted 5,6-/5,7-Dichloro-3-methyl-4*H*-1,4-benzothiazinesulfones.

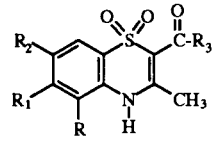
A solution of 4*H*-1,4-benzothiazine **4** (0.01 mole) in glacial acetic acid (15 ml) was placed in a two necked round bottom flask (50 ml) equipped with a reflux condenser and dropping funnel. Hydrogen peroxide (30%, 5 ml) was added to the reaction mixture dropwise at room temperature and refluxed for 15 minutes at 60-70°. As the colour of the solution turns yellow, heating was stopped and another lot of hydrogen peroxide (5 ml) was added. The refluxing was continued for 3-4 hours. The excess solvent was removed by distillation under reduced pressure and poured into a beaker containing crushed ice. The yellow residue obtained was filtered, washed with water successively and crystallized from ethanol. Physical data of 4*H*-1,4-benzothiazine sulfones synthesized are tabulated in Table 2.

Infrared Spectra.

The N-H stretching vibrations appear as sharp intense peaks at 3190-3340 cm^{-1} in all 4*H*-1,4-benzothiazines and are shifted to slightly higher frequency (3200-3445 cm^{-1}) in the corresponding sulfones. A sharp band appears in the region 1560-1620 cm^{-1} due to the C=O stretching vibrations in 4*H*-1,4-benzothiazines and shifts towards higher frequency region 1600-1680 cm^{-1} in the corresponding sulfones are observed. This is in agreement with increased electron acceptor ability of the heteroaromatic nucleus in the sulfones as compared to the parent nucleus. In sulfones the lone pair of the nitrogen atom is withdrawn more effectively towards the ring, it conjugates less effectively with the carbonyl group and this results in higher carbonyl group frequencies. The −I effect of the SO_2 group combined with the mesomeric effect operating in the same direction also hinders the conjugation of

Table 2

Physical Data of 4*H*-1,4-Benzothiazinesulfones **5a-o**



	Compound				MP	Yield	Molecular	% Calcd./Found		
	R	R_1	R_2	R_3	°C	%	Formula	C	H	N
I	II	III	IV	V	VI	VII	VIII	IX	X	XI
5a	Cl	Cl	H	CH_3	122-124	38	$C_{11}H_9NSO_3Cl_2$	43.13 43.34	2.94 2.93	4.57 4.55
5b	Cl	H	Cl	CH_3	120-126	62	$C_{11}H_9NSO_3Cl_2$	43.13 42.93	2.94 2.93	4.57 4.58
5c	Cl	Cl	H	OCH_3	112-115	45	$C_{11}H_9NSO_4Cl_2$	40.99 41.19	2.79 2.80	4.34 4.32
5d	Cl	H	Cl	OCH_3	208-210	71	$C_{11}H_9NSO_4Cl_2$	40.99 40.79	2.79 2.78	4.34 4.36
5e	Cl	Cl	H	OC_2H_5	102-104	36	$C_{12}H_{11}NSO_4Cl_2$	42.85 43.06	3.27 3.28	4.16 4.14
5f	Cl	H	Cl	OC_2H_5	112-115	41	$C_{12}H_{11}NSO_4Cl_2$	42.85 42.64	3.27 3.26	4.16 4.18
5g	Cl	Cl	H	C_6H_4Cl (*p*)	94-98	67	$C_{16}H_{10}NSO_3Cl_3$	47.70 47.93	2.48 2.49	3.47 3.48
5h	Cl	H	Cl	C_6H_4Cl (*p*)	110-113	53	$C_{16}H_{10}NSO_3Cl_3$	47.70 47.47	2.48 2.47	3.47 3.46
5i	Cl	Cl	H	C_6H_4Br (*p*)	202-205	58	$C_{16}H_{10}NSO_3Cl_2Br$	42.95 43.16	2.23 2.24	3.13 3.14
5j	Cl	H	Cl	C_6H_4Br (*p*)	196-198	64	$C_{16}H_{10}NSO_3Cl_2Br$	42.95 42.74	2.23 2.24	3.13 3.12
5k	Cl	Cl	H	C_6H_4F (*p*)	204-207	39	$C_{16}H_{10}NSO_3Cl_2F$	49.74 49.99	2.59 2.60	3.62 3.61
5l	Cl	Cl	H	$C_6H_4CH_3$ (*p*)	120-123	55	$C_{17}H_{13}NSO_3Cl_2$	53.40 53.66	3.40 3.41	3.66 3.68
5m	Cl	Cl	H	$C_6H_4OCH_3$ (*p*)	154-157	69	$C_{17}H_{13}NSO_4Cl_2$	51.25 51.50	3.26 3.25	3.51 3.50
5n	Cl	Cl	H	$C_6H_4OCH_3$ (*m*)	118-121	48	$C_{17}H_{13}NSO_4Cl_2$	51.25 50.99	3.26 3.24	3.51 3.50
5o	Cl	Cl	H	$C_6H_3(OCH_3)_2$ (*m*,*p*)	95-98	64	$C_{18}H_{16}NSO_5Cl_2$	50.34 50.59	3.72 3.71	3.26 3.25

the lone pair of electrons at the nitrogen atom with the carbonyl group. The asymmetric stretching mode of the sulfonyl group in all sulfones appears as sharp peak at 1370-1390 cm^{-1} in carbon tetrachloride, while in the solid state this absorption band splits into three bands and appears in the regions, 1375-1392 cm^{-1}, 1295-1320 cm^{-1} and 1230-1270 cm^{-1}. The asymmetric stretching vibrations in the sulfone is strongly affected on passing from solution to the crystalline state. The symmetrical stretching vibrations of the sulfonyl group are observed as a doublet (in some cases as broad signal) in the region 1120-1170 cm^{-1} in potassium bromide discs whereas in solution it appears at 1122-1168 cm^{-1}. These frequencies are slightly affected by the state of aggregation. The two sharp absorption bands in benzothiazines and their sulfones are observed in the region 1350-1380 cm^{-1} and 1445-1490 cm^{-1} due to the asymmetric and symmetric C-H deformation vibrations of the $C-CH_3$ group. Peaks corresponding to C-Cl stretching vibrations appear at 710-780 cm^{-1} in the benzothiazines as well as in the sulfones.

NMR Spectra.

Resonance signal due to the NH proton in benzothiazines appears at δ 7.96-8.56 and is shifted downfield (δ 8.04-8.76) in the corresponding sulfones. In benzothiazines **4a-o** the signal due to the allylic linkage ($C=C-CH_3$) appears in the range δ 1.89-2.64 and is also shifted downfield (δ 2.14-2.85) in sulfones. Triplets and quartets due to the carboethoxy group at C_2 in benzothiazines **4c-f** are centered in the regions δ 1.23-1.24 and δ 3.60-4.24 respectively and are also shifted downfield (δ 1.24-1.85 and δ 4.13-4.46) in sulfones **5c-f**. A singlet due to the CH_3 protons at the *para* position in the benzoyl side chain at C_2 in benzothiazine **4l** is shifted in the corresponding sulfone **5l** from δ 1.89 to δ 1.91. Resonance signal due to the OCH_3 protons at the *para* and *meta*

positions in the benzoyl side chain at C_2 in benzothiazines **4m** and **4n** is also shifted downfield (from δ 3.60 and δ 3.78 to δ 3.82 and δ 3.87 respectively) in corresponding sulfones **5m** and **5n**. Two signals obtained at δ 3.78 and δ 3.82 in benzothiazines **4o** due to two methoxy groups at the *m*- and *p*-positions in the benzoyl side chain at C_2 are shifted to downfield (δ 3.87 and δ 4.04) in the corresponding sulfone **5o**. Conversion of benzothiazines to sulfones involves conversion of the sulfide linkage to sulfoxide and results in shifting resonance signals downfield. It is due to decreased local diamagnetic shielding of the substituent attached to the thiazine ring and also to diamagnetic anisotropic deshielding. In sulfones, the thiazine nucleus contains large closed loops of π electrons in comparison to the parent benzothiazine due to the conversion of the sulfide linkage to the dioxide, in which strong diamagnetic currents are induced by the magnetic field. This effect results in an increased ring current effect causing the deshielding of aromatic protons and any group contained in the plane of the thiazine nucleus.

Mass Spectra.

The mass spectrum of each benzothiazine shows a molecular ion peak in accordance with its molecular weight. In each case the side chain at C_2 appeared as the base peak (Scheme 3).

REFERENCES AND NOTES

[1] R. R. Gupta, ed, Phenothiazines and 1,4-Benzothiazines. Chemical and Biomedical Aspects, Elsevier, Amsterdam, 1988.

[2] H. Keyzer, G. M. Eckert, I. S. Forrest, R. R. Gupta, F. Gutmann and J. Molnar, eds, Thiazines and Structurally Related Compounds, Proceedings of the Sixth International Conference on Phenothiazines and Structurally Related Psychotropic Compounds, Pasadona, California, September 11-14, 1990, Kriger Publishing Company Malabar, Florida, 1992.

[3] Y. Chihara, S. Setoguchi and O. Yaoka, Japanese Patent 8,403,770, (1984); *Chem. Abstr.*, **103**, 54090 (1985).

[4] J. Iwao, T. Iso and M. Oya, European Patent 166,386 (1984); *Chem. Abstr.*, **102**, 24637 (1985).

[5] C. Sastry, V. Reddy, B. Ram, M. Jogibhukta, V. S. H. Krishanan, A. N. Singh, J. G. Reddy, S. C. Chaturvedi, S. P. Rao and D. R. Shridhar, *Indian J. Chem.*, **28(B)**, 52 (1989).

[6] R. R. Gupta, R. K. Rathore, V. Gupta and R. S. Rathore, *Pharmazie*, **46**, 602 (1991).

[7] D. D. Bhatnagar, K. K. Gupta, V. Gupta and R. R. Gupta, *Curr. Sci.*, **58**, 1091 (1989).

[8] V. Gupta and R. R. Gupta, *J. Prakt. Chem.*, **333**, 153 (1991).

[9] R. R. Gupta, R. K. Gautam and R. Kumar, *Heterocycles*, **22**, 1143 (1984).

[10] R. R. Gupta, S. K. Jain, V. Gupta and R. K. Rathore, *Pharmazie*, **44**, 572 (1989).

[11] R. R. Gupta, R. S. Rathore, M. Jain and V. Saraswat, *Pharmazie*, **47**, 229 (1992).

[12] C. R. Rasmussen, U. S. Patent 3,476,749 (1969); *Chem. Abstr.*, **72**, 217227 (1970).

[13] G. Fengler, D. Arlt, K. Groche, H. J. Zeiler and K. Metzger, German Offen. 3,229,125 (1984); *Chem. Abstr.*, **101**, 7176 (1984).

[14] H. Zenno and T. Mizutani, Japanese Patent 7,006,262 (1970); *Chem. Abstr.*, **72**, 132759 (1970).

[15] H. Zinnes, M. Schwartz and J. Shavel, Jr., German Offen. 2,208,351 (1972); *Chem. Abstr.*, **77**, 164722 (1972).

[16] K. H. Mayer and A. Haberkorn, German Offen. 2,020,298 (1971); *Chem. Abstr.*, **76**, 72533 (1972).

[17] G. Fengler, D. Arlt and K. Groche, German Offen, 3,329,124 (1984); *Chem. Abstr.*, **101**, 90953 (1984).

[18] G. Filacchioni, V. Nacci and G. Stfanrich, *Farmaco. Ed. Sci.*, **31**, 478 (1976); *Chem. Abstr.*, **85**, 143048 (1976).

[19] Vandana Saraswat, Ph.D. Thesis, University of Rajasthan, Jaipur, India, 1992.